Synthesis of linear diphenyl furanocoumarins

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Abstract

The elegant and direct synthesis of linear 2',3'-diphenyl furano-
coumarins is recorded for the first time by submitting the desyl ether of
hydroxycoumarins to the action of mild 0.1 N KOH. This reagent
brings about aldol condensation followed by cyclisation and dehydration
in the presence of acids as proposed by Macleod and Worth to give the
desired linear diphenyl furanocoumarins in good yield.

1. Introduction

The synthesis of 2',3'-diphenyl furanocoumarins with the furan ring annu-
lated in the 5, 6/7, 8 (angular) and 6, 7 (linear) positions to serve as model
compounds with the cyclised triarylethylene structure so essential for anti-
fertility activity has earlier been recorded. These compounds could be
synthesised by condensing the appropriate hydroxycoumarin with benzoin
in the presence of polyphosphoric acid (PPA). It must be pointed out that
for the synthesis of the linear (6, 7) isomer, however, a blocking group like
the methyl group at the 8-position had to be employed so as to direct the
mode of ring closure in the desired fashion. Now a direct and convenient
synthesis of the linear isomer without the use of a blocking group and
employing a different sequence of reactions has been worked out. This is
based on the observations of Macleod and Worth that 7-O-acetonyl/aceto-
phenyl ether of 7-hydroxycoumarin and 7-hydroxy-4-methyl-coumarin when
submitted to the action of 0.1 N KOH gives in a single step and in high
yield the linear β-substituted (alkyl/aryl) furanocoumarin related to psoralen,
the well known linear furanocoumarin.

Based on the above observations, attempts have now been made to
synthesize linear fused 2',3'-diphenyl furanocoumarins. As model experi-
ments, 7-hydroxycoumarin, 3 7-hydroxy-4-methylcoumarin and 7-hydroxy-

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4-phenylcoumarin\(^5\) have been condensed with desyl bromide in acetone medium in presence of potassium carbonate to yield the 7-O-desyl ethers. These on heating with 0.1 N potassium hydroxide followed by acidification have yielded the linear 2', 3'-diphenyl (6, 7: 4': 5') furanocoumarins in good yields (50\%). The linear structure proposed for these compounds is based on the NMR spectra as recorded in the experimental section.

This novel synthesis of the linear 2', 3'-diphenyl furano compound is visualised to proceed by the following mechanism (vide chart) on analogy with the one proposed by Macleod and Worth (\textit{loc. cit.}):

(a) base hydrolysis of the pyrone ring to form the phenoxide ion; (b) intramolecular aldol condensation between the exocyclic carbonyl function and the resonance stabilized carbonion generated at the \(p\)-position to the phenoxide ion; (c) abstraction of a proton from the newly formed ring junction leading to the coumarinic acid salt; (d) reformulation of the pyrone ring on acidification; (e) spontaneous elimination of water from the labile \(\beta\)-hydroxydihydrofuran to give the 2', 3'-diphenyl furan derivative.

2. \textbf{Experimental}

Melting points are uncorrected. Ultraviolet spectra were recorded on a Beckmann DU spectrophotometer and infrared spectra on a Perkin-Elmer 237 instrument. The NMR spectra were measured on a Varian A-60 spectrometer using tetramethylsilane as internal reference.

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I. 7-O-Desylcoumarin

7-Hydroxycoumarin (1·62 g) in acetone (150 ml) was treated with desyl bromide (2·75 g) and potassium carbonate (5 g) and the mixture refluxed for 12 hr. The inorganic salts were filtered off and the solvent distilled off from the filtrate. The crude desyl ether thus obtained crystallised from alcohol as rods, m.p. 160° C. (3·0 g, 84·5%). Found: C, 77·82; H, 4·25%. Cal. for C_{20}H_{16}O_{4}: C, 77·54; H, 4·49%. $\lambda_{\text{max}}$ (MeOH) 247 nm ($\log \epsilon = 4·25$); 295 (4·12). $\nu_{\text{max}}$ (KBr) 1720 (lactone carbonyl), 1690 (acyl carbonyl), 1610, 1260, 1270 cm$^{-1}$.

II. 2, 3-Diphenyl-7-oxo-7 H furo (2, 3-g) (1) benzopyran

7-O-Desylcoumarin (1·0 g) was treated with KOH (0·1 N; 400 ml) and refluxed for 6 hr. The aqueous alkaline solution was filtered from the small amount of insoluble matter and then acidified. 2, 3-Diphenyl-7-oxo-7 H-furo (2, 3-g) (1) benzopyran that separated crystallised from alcohol as shining needles, m.p. 248-49° C. (0·5 g, 52·8%). Found: C 81·45; H, 3·95. Cal. for C_{23}H_{14}O_{3}: C, 81·66; H, 4·14%. $\lambda_{\text{max}}$ (MeOH) 235 nm ($\log \epsilon = 3·33$); 285 (4·60); 344 (3·82). $\nu_{\text{max}}$ (KBr) 1710 (lactone carbonyl) 1595, 1550, 1425, 865, 845, 830 cm$^{-1}$. NMR (DMSO) $\delta$ 6·29 (one-proton doublet, J 10 Hz, H 6); 8·0 (one-proton doublet, J 10 Hz, H 5) 7·71 (one-proton singlet, H 4) 7·3-7·57 (eleven-proton multiplet, 2, 3 phenyl and H 9).

III. 7-O-Desyl-4-methylcoumarin

7-Hydroxy-4-methylcoumarin (1·76 g) in acetone (150 ml) on refluxing with desyl bromide (2·75 g) and potassium carbonate (5·0 g) for 12 hrs yielded the O-desyl ether (III) as needles, m.p. 178-80° C. (3·3 g, 94·5%). Found: C, 77·83; H, 4·04. Cal. for C_{24}H_{18}O_{4}: C, 77·70; H, 4·00%. $\lambda_{\text{max}}$ (MeOH) 246 nm ($\log \epsilon = 4·24$); 295 (4·07). $\nu_{\text{max}}$ (KBr) 1720 (lactone carbonyl), 1670 (acyl carbonyl), 1601, 1250 cm$^{-1}$.

IV. 2,3-Diphenyl-5-methyl-7-oxo-7 H furo (2,3-g) (1) benzopyran

7-O-Desyl-4-methylcoumarin (0·8 g) was refluxed with KOH (0·1 N; 300 ml) for 6 hr and the reaction mixture worked up as in the case of 7-hydroxycoumarin. The furan compound (IV) crystallised from alcohol as needles, m.p. 225°. (0·25 g, 52%). Found: C, 82·2; H, 4·3. Cal. for C_{24}H_{18}O_{2}: C, 81·8; H, 4·6%. $\lambda_{\text{max}}$ (MeOH) 240 nm ($\log \epsilon = 4·35$); 282 (4·57). $\nu_{\text{max}}$ (KBr) 1730 (lactone carbonyl), 1575, 1450, 1440, 1435, 865, 850, 840 cm$^{-1}$. NMR (CDCl$_3$) $\delta$ 2·45 (three-proton doublet, J 1·8 Hz, 5 methyl); 6·28 (one-proton doublet, J 1·8 Hz, H 6); 7·30 (one-proton
singlet H 9); 7·63 (one-proton singlet, H 4); 7·35-7·56 (ten-proton multiplet, 2, 3-phenyl protons).

V. 7-O-Desyl-4-phenylcoumarin

7-Hydroxy-4-phenylcoumarin (2·38 g) in acetone (130 ml), desyl bromide (2·75 g) and potassium carbonate (5·0 g) were refluxed for 12 hr. to yield 7-O-Desyl-4-phenylcoumarin. Recrystallisation from benzene yielded colourless needles melting at 186°-90°C. (3·5 g, 81%) Found: C, 80·2; H, 5·0. Cal. for C_{29}H_{20}O_{4}: C, 80·6; H, 4·6%. λ_{max} (MeOH) 234 nm (log ε = 4·30); 283 (4·47); 347 (4·3). ν_{max} (Nujol) 1725 (lactone carbonyl), 1690 (acyl carbonyl) cm⁻¹.

VI. 2,3,5-Triphenyl-7-oxo-7 H-furo (2,3-g) (1) benzopyran

7-O-Desyl-4-phenylcoumarin (1·5 g) was refluxed with KOH (0·1 N) (aq. dioxane 3:1) 400 ml for 6 hr and the reaction mixture worked up as in the case of compounds II and IV. 2,3,5-Triphenyl-7-oxo-7 H-furo (2,3-g) (1) benzopyran thus obtained recrystallised from benzene as colourless needles melting at 244-46°C. (0·9 g, 62%). Found: C, 83·7; H, 4·6. Cal. for C_{29}H_{18}O_{3}: C, 84·0; H, 4·4%. λ_{max} (MeOH) 233 nm (log ε = 4·58); 291 (4·70); 353 (4·32). ν_{max} (Nujol) 1740 (lactone carbonyl), 1570, 1460, 1450, 1375, 1340, 885, 865, 825 cm⁻¹. NMR (CDCl) δ 6·37 (one-proton singlet, H 6); 7·35 (one-proton singlet, H 9); 7·66 (one-proton singlet, H 4); 7·38-7·55 (fifteen-proton multiplet, 2,3,5-phenyls).

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